

# VARIABLE HEAVY DOMAIN

		10	20	30	40
2C4	EVQLQQSGPELVKPGTSVKISKAS	[GFTFTDYTMD]	WVKQS		
	** ** *	* * * *	*	*	*
574	EVQLVESGGGLVQPGGSLRLSCAAS	[GFTFTDYTMD]	WVRQA		
		** *	*	*	*
hum III	EVQLVESGGGLVQPGGSLRLSCAAS	[GFTFSSYAMS]	WVRQA		

		50	a	60	70	80
2C4	HGKSLEWIG	[DVNPNSGGSIYNQRFKG]	KASLTVD	RSSRIVYM		
	* *	**	***	*	****	*
574	PGKGLEWVA	[DVNPNSGGSIYNQRFKG]	RFTLSVDRSKNTLYL			
		*****	***	****	*	*
hum III	PGKGLEWVA	[VISGDGGSTYYADSVKG]	RFTISRDN	SKNTLYL		

		abc	90	100ab	110
2C4	EIRSLTFE	TAVYYCAR	[NLGPSFYFDY]	WGQGT	TLTVSS
	***	**		**	
574	QMNSLRAED	TAVYYCAR	[NLGPSFYFDY]	WGQGT	TLTVSS
			*****		
hum III	QMNSLRAED	TAVYYCAR	[GRVGYSLYDY]	WGQGT	TLTVSS

FIG. 1

# Variable Light Domain

	10	20	30	40
2C4	DTVMTQSHKIMSTSVGDRVSITC	[KASQDVSIGVA]	WYQQRP	*
	**	**** *		
574	DIQMTQSPSSLASASVGDRVTITC	[KASQDVSIGVA]	WYQQKP	*
		* ** ***		
hum KI	DIQMTQSPSSLASASVGDRVTITC	[KASQDVSIGVA]	WYQQKP	
	50	60	70	80
2C4	GQSPKLLIY [SASYRYT]	GVPDRFTGSGSGTDFTFTISSVQA	*	*
	**	* *		
574	GKAPKLLIY [SASYRYT]	GVPSRFTGSGSGTDFTLTISLQ		
	* ****			
hum KI	GKAPKLLIY [AASSLES]	GVPSRFTGSGSGTDFTLTISLQ		
	90	100		
2C4	EDLAVYYC [QQYIYPYT]	FGGQKLEIKRT		
	* *	* *		
574	EDFATYYC [QQYIYPYT]	FGQGTKVEIKRT		
	*** *			
hum KI	EDFATYYC [QQYNSLPWT]	FGQGTKVEIKRT		

FIG. 2

Maytansinoids  
(DM1)

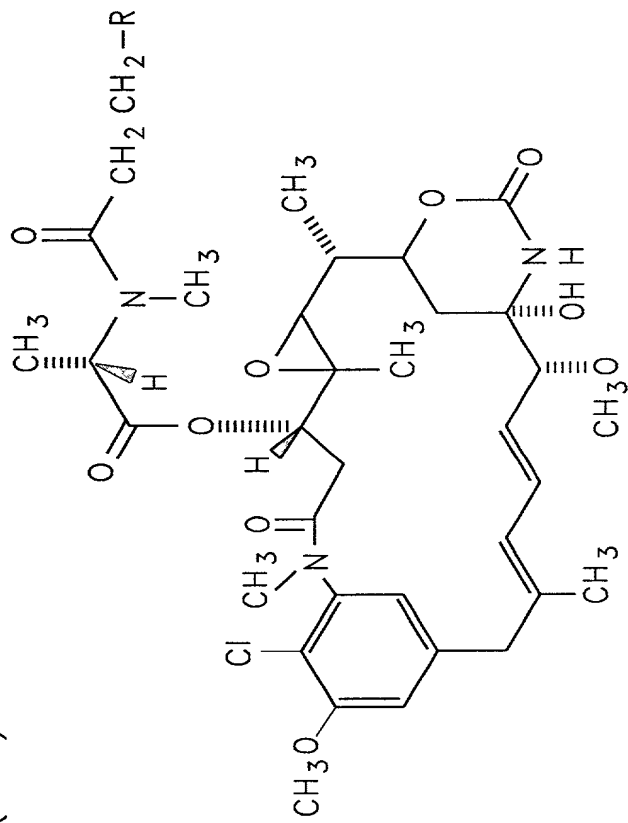
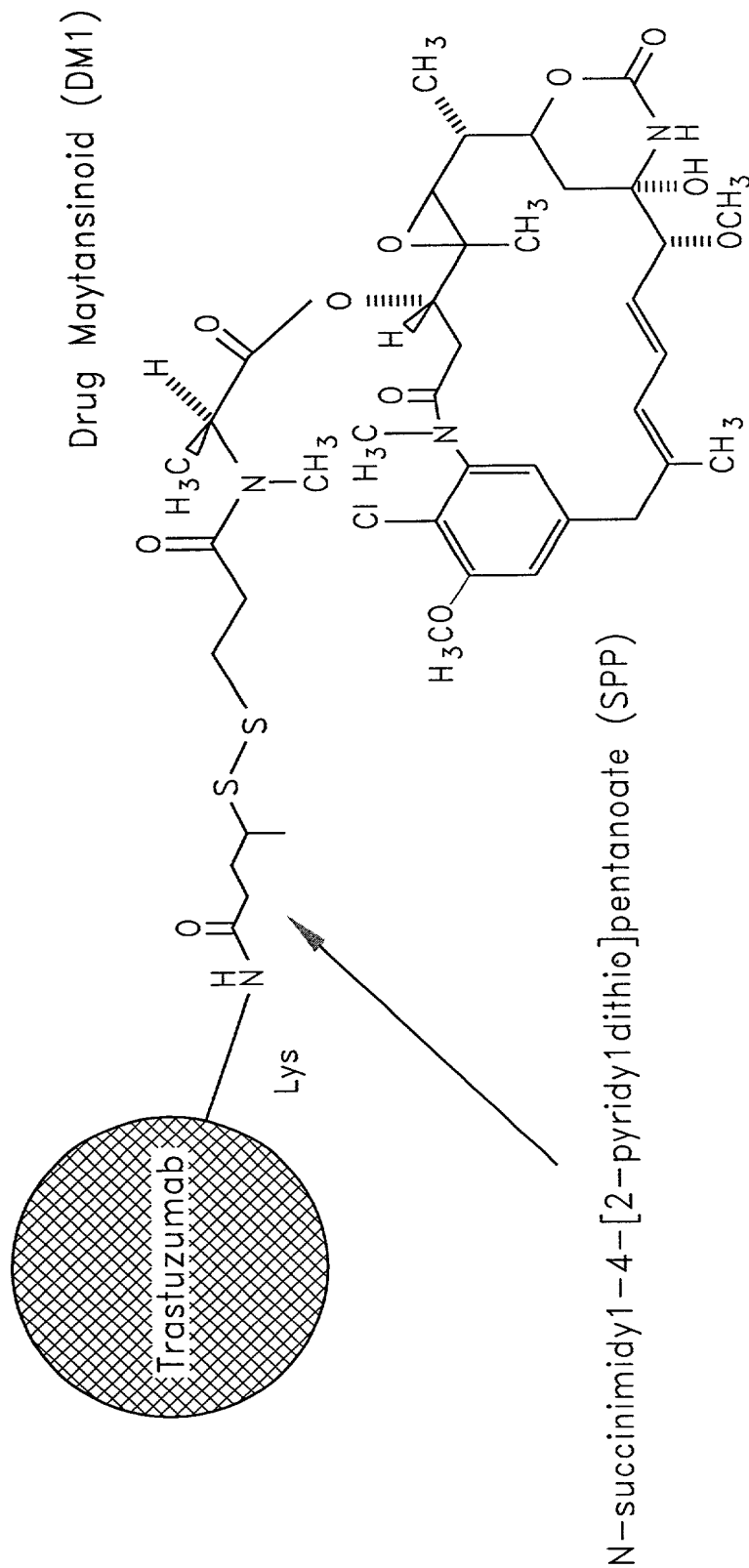


FIG. 3

[illegible]

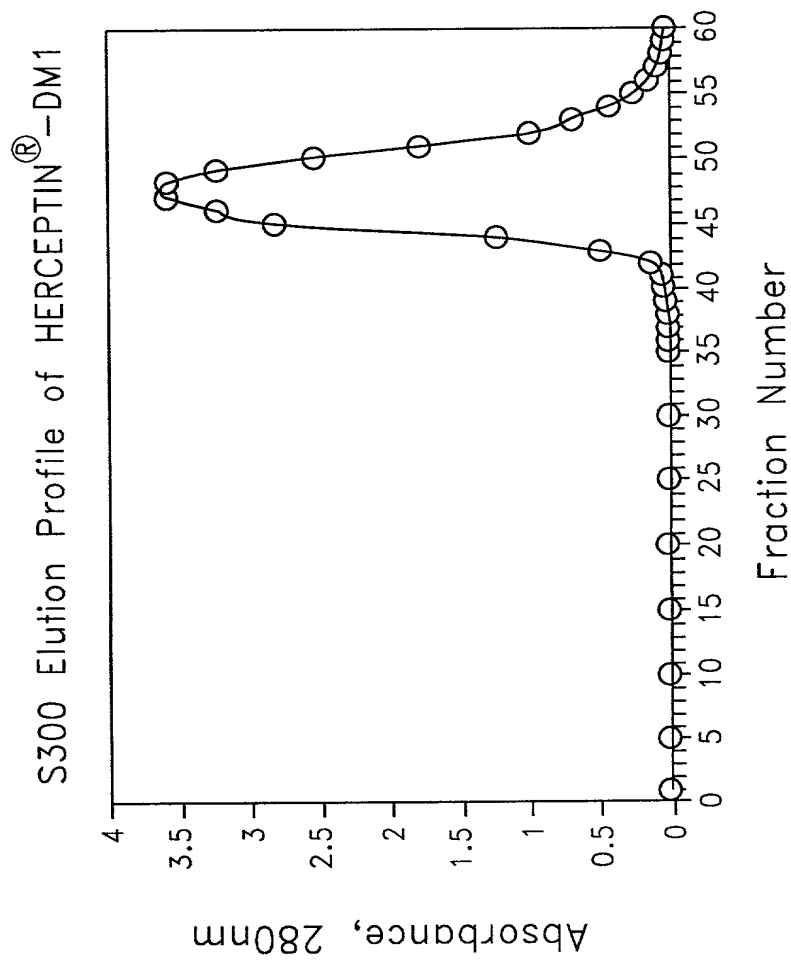


FIG. 5

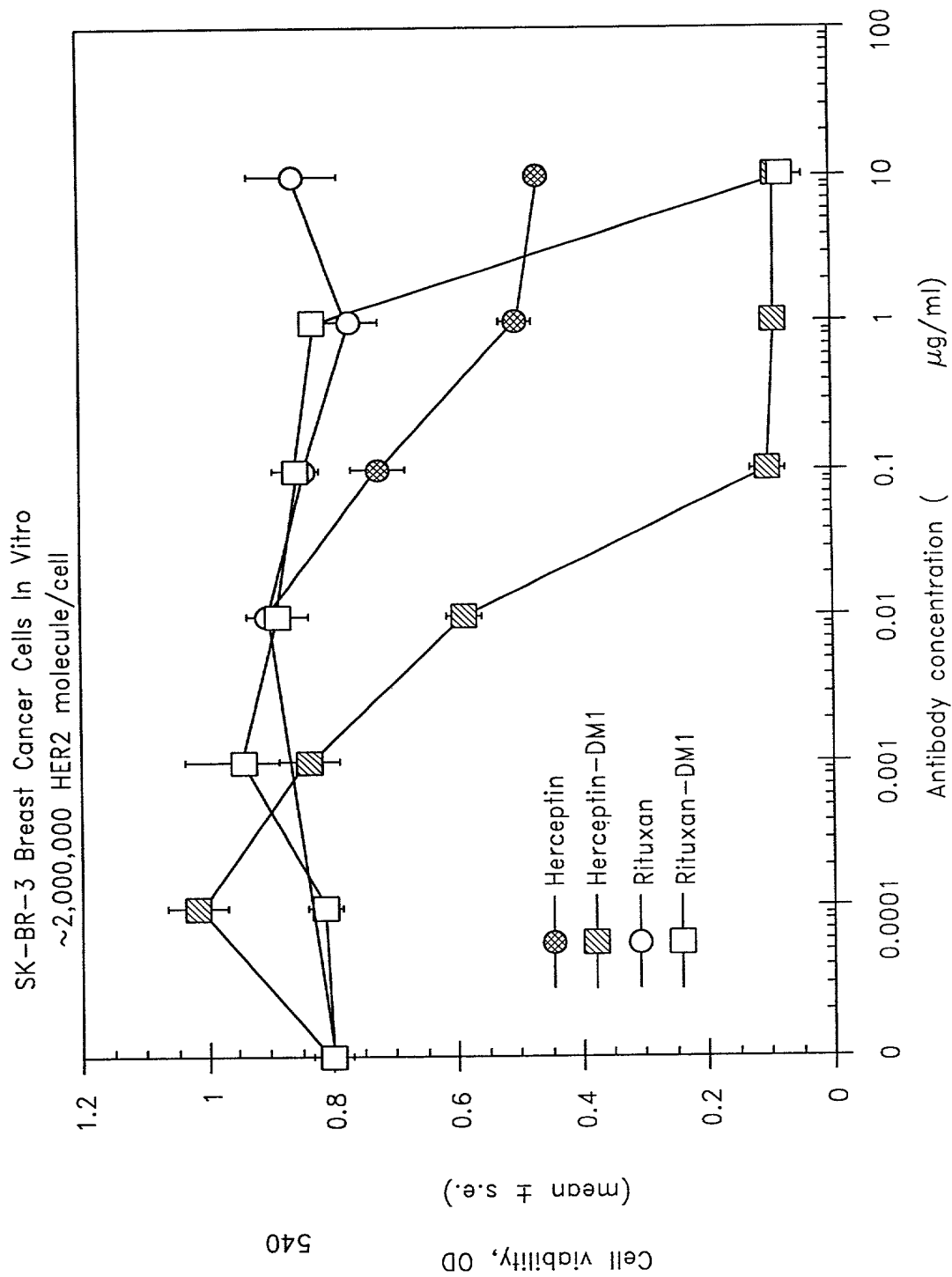


FIG. 6







rmaI  
 maeI  
 bfaI  
 pleI  
 hinfi  
 aluI  
 mnli  
 styI  
 bsaJI  
 bsmAI  
 mboII  
 nlaIII  
 rsaI  
 csp6I  
 nlaIII  
 rmaI  
 maeI  
 bfaI  
 bsmI  
 801 AAAGACTCGC CAGAGCTAGA CCTCCTTGGT GTATGTTGTC TCAAGAAGAA AAAGACGACA TGAACAACA GGTACATGAT TATATTTATC TAGGAACAGG  
 TTTCTGAGCG GTCTCGATCT GGAGGAACCA CATAACAACAG AGTTCTTCTT TTTCTGCTGT ACTTTGTTGT CCATGTAATA ATATAAATAG ATCCTTGTCC  
  
 tspRI  
 styI  
 bsli  
 bsli  
 bsaJI  
 mnli  
 alw26I/bsmAI  
 901 AATGCACCTT TGGGGAAGA TTTTCCATAC CAAGGAGGG ACAGTGGCTG GACTAATAGA ACATTATTCT GCAAAAACTT ATGGCATGAG TTATTATGAA  
 TTACGTGAAA ACCCCTTTCT AAAAGGTATG GTTCTCTCCC TGTCACCGAC CTGATTATCT TGTAAATAAGA CGTTTTTGAA TACCGTACTC AATAATACTT  
  
 tru9I  
 msel  
 styI  
 nlaIV  
 aciI  
 bsaJI  
 afliI/bfRI  
 maeIII  
 msel  
 mnli  
 bsmAI  
 001 TAGCCTTTAT TGGCCCAACC TTGCGGTTCC CAAGGCTTAA GTAAGTTTTT GGTACAAAC TGTTCCTTAA ACAGGATGT GAGACAAAGT CTTTGGTGAC  
 ATCGGAAATA ACCGGTTGG AACGCCAAGG GTTCCGAATT CATTCAAAAA CCAATGTTG ACAAGAAATT TGCTCCTACA CTCTGTTTAC CAAAGGACTG  
  
 sstI  
 sacI  
 hgiJII  
 hgiAI/aspHI  
 ecl136II  
 bsp1286  
 bsiHKA  
 bmyI  
 ddeI  
 sau3AI  
 mboI/ndeII  
 dpnII aluI  
 dpnI banII ddeI  
 101 TTGGTTTGGT ATCAAAGGTT CTGATCTGAG CTCTGAGTGT TCTATTITCC TATGTTCTTT TGGAAATTTAT CCAAAATCTTA TGTAATGCT TATGTAAACC  
 AACCAAACCA TAGTTTCCAA GACTAGACTC GAGACTCACA AGATAAAGG ATACAAGAAA ACCTTAAATA GGTTTAGAAT ACATTACGA ATACATTTGG

FIG. 7C

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                bsmAI
                esp3I
                foki bsmBI bsrBI tsp45I
                bstF5I aciI maeIII
201 AAGATATAAA AGAGTGCTGA TTTTGTGAGT AAACCTGCAA CAGTCCTAAC ATTACACCTCT TGTGTGTTTG TGTCTGTTTG CCATCCCGTC TCCGCTCGTC
TTCATATATT TCTCAGGACT AAAAACTCA TTGAACGTT GTCAGGATTG TAAGTGAGA ACACACAAAC ACAGACAAGC GGTAGGGCAG AGCGAGCAG

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                fnu4HI/bsofI
                haeIII/palI
                mcrI
                eagI/xmaIII/ecI XI
                eaeI
                notI
                fnu4HI/bsofI scfI
                cac8I cfrI tru9I
                pstI
                aluI aciI aciI
                hindIII bsiEI mselI bsgI
301 ACTTATCCTT CACTTTCCAG AGGGTCCCC CGCAGACCCC GGATCGCTAG CTCGGCAATC GATAGCTTG CGCCCGCTTA ACTGCAGAAG TTGGTCGTGA
TGAATAGGAA GTGAAAGGC TCCAGGGGG GCGTCTGGG CCTAGCGATC GAGCGCTTAG CTATTCGAAC GCCGGCGAAT TGACGTCTTC AACCAAGCACT
                ^start of BS intron insert at Cla
                ^bp820 in pCI
                ^start of BS insert at HindIII

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                pleI
                hinfi
                mboII
                bpuAI
                bbsI
                bsmAI
                taqI
                bsrI
                bsaI
                maeIII
                mselI
                tru9I bsmAI
                maeIII
                mselI
                bsaI
                bsrI
                bspMI
                tspRI
401 GGCACCTGGC AGGTAAGTAT CAAGGTACA AGACAGGTTT AAGGAGACCA ATAGAACTG GGCTTGTGCA GACAGAGAAG ACTCTGCGT TTCTGATAGG
CCGTGACCG TCCATTCATA GTTCCAATGT TCTGTCCAAA TTCTCTGCTGATCTTGAC CCGAACAGCT CTGTCTCTTC TGAGAAGCA AAGACTATCC
                ^start of chimeric intron at pCI 857

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FIG. 7D

501 CACCTATTGG TCTTACTGAC ATCCACTTTG CCTTCTCTC CACAGGTGTC CACTCCCAGG TTCAATTACA GCTCTTAAGC GGCCGCAAGC TTGATATCGA GTGGATAACC AGAATGACTG TAGGTGAAC GGAAGAGAG GTGTCCACAG GTGAGGTCC AAGTTAATGT CGAGAAATCG CCGCGTTTCG AACTATAGCT

^end of chimeric intron at pCI 989

end of BS insert at HindIII^

601 ATTCTGTCAG CCCGGGGGAT CCACHTAGTGG ATCCAAAGAA TTCAAAAAGC TTCTCGAGGG CGCGCGCGCG GCCCCCCACCC CTCGCAGCAC CCCGCGCGCCC  
TAAGGACGTC GGGCCCCCTA GGTGATCACC TAGGTTTCTT AAGTTTTTCG AAGAGCTCCC GCGCGCGGCG CGGGGGTGGG GAGCGTCGTG GGGCGCGGGG



haaeIII/pali  
eaeI  
cfrI  
scrFI  
mvaI  
ecoRII  
dsaV  
bstNI  
bssKI  
apyI  
rmaI  
maeI  
bsaI  
bsmAI mspAI/nsbII  
bsaI acil  
bsaJI  
mnli  
alul  
mnli  
alul  
mnli  
tset  
fnu4HI/bsoFI  
bbvI  
tspRI  
ecoO109I/draII  
mnli  
acil  
gagGTGCGG  
ATTGTGCGAG  
GCACCCAGCT  
CTTTGAGGAC  
AACTATGCC  
CTTGAGGCTGT  
AGACAATGGA  
GACCCGCTGA  
GTGAGGCAGG  
TCCCAGTGCA  
GAGGTGCGG  
CTCCGACGCC  
TAACACGCTC  
CGTGGGTGCA  
GAAACTCCTG  
TTGATACGGG  
ACCGCACGA  
TCTGTACCT  
CTGGGCGACT  
91 V R Q V P L Q R L R I V R G T Q L F E D N Y A L A V L D N G D P L N

[illegible][illegible]

**FIG. 7G**



[illegible]

**FIG. 7I**

[illegible]

-425









[illegible]

FIG. 7N

[illegible]

FIG. 70





bslI	rsal	scrFI	bslI	bsaJI	mmol	sau96I	alul	scrFI
csp6I	nlaIV	mspI	bslI	bsaJI	bslI	avaII	tseI	mval
kpnI	hgiCI	hpaII	alwNI	bslI	alwNI	bslI	fnu4HI/bsaFI	ecoRII
hgiCI	asp718	dsav	alw26I/bsmAI	haeII	alw26I/bsmAI	haeII	hgiCI	dsav
acc65I	acc65I	cauII	alw26I/bsmAI	haeII	alw26I/bsmAI	haeII	hgiCI	bsaJI
4801	TGGTACCCCA	bsaJI	alw26I/bsmAI	haeII	alw26I/bsmAI	haeII	hgiCI	bsaJI
1025	V P Q Q G F F C P D P A P G A G G M V H H R H R S S S T R S S G G G	bsaJI	alw26I/bsmAI	haeII	alw26I/bsmAI	haeII	hgiCI	bsaJI

sau96I	rmaI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI
avaII	maeI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI
asuI	bfaI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI
4901	GGACCTGACA	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI
1058	D L T L G L E P S E E A P R S P L A P S E G A G S D V F D G D L	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI	bsmAI

FIG. 7R





Year	1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099
1970	1971	1972	1973	1974	1975	1976	1977	1978	1979	1980	1981	1982	1983	1984	1985	1986	1987	1988	1989	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015	2016	2017	2018	2019	2020	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	2031	2032	2033	2034	2035	2036	2037	2038	2039	2040	2041	2042	2043	2044	2045	2046	2047	2048	2049	2050	2051	2052	2053	2054	2055	2056	2057	2058	2059	2060	2061	2062	2063	2064	2065	2066	2067	2068	2069	2070	2071	2072	2073	2074	2075	2076	2077	2078	2079	2080	2081	2082	2083	2084	2085	2086	2087	2088	2089	2090	2091	2092	2093	2094	2095	2096	2097	2098	2099	

1



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rmaI      mspI
maeI      hpaiI
bfai      scrFI
sau96I    nciI
avaII     dsav
asuI      cauII
          bssKI
          bslI
          tseI bslI
          fnu4HI/bsoFI
          mnlI mboII bsaJI bsrI bglII scfI taqI
          ppuMI mnlI          bstFI
          eco0109I/draII sfaNI
          AGGACCTAGA GGAAGGCATC CAAACGCTGA TGGGGAGGCT GGAAGATGGC AGCCCCCGGA CTGGGCAGAT CTTCAAGCAG ACCTACAGCA AGTTCGACAC
          TCCTGGATCT CCTTCCGTAG GTTGGCGACT ACCCTCCGA CCTTCTACCG TCGGGGGCCT GACCCGTCTA GAAGTTCGTC TGGATGTCGT TCAAGCTGTG
701
^end of ex 4/ start ex 5

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801 AAATCAGAC AACGATGAG CACTACTCAA GAACTACGGG CTGCTCTACT GCTTCAGGAA GGACATGGAC AAGGTCGAGA CATTCTCTGG CATCGTGCAG
TTTGAGTGTG TTGCTACTGC GTGATGAGTT CTTGATGCCC GACGAGATGA CGAAGTCCTT CCTGTACCTG TTCCAGCTCT GTAGGACGC GTAGCAGTC

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FIG. 7V











[illegible]

**FIG. 7AA**



[illegible]

FIG. 7CC

[illegible]

**FIG. 7DD**







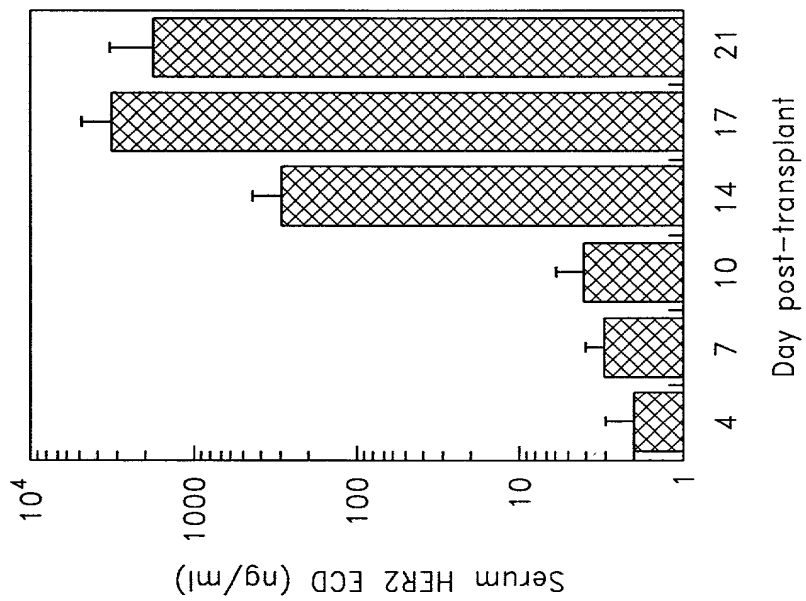


FIG. 8A

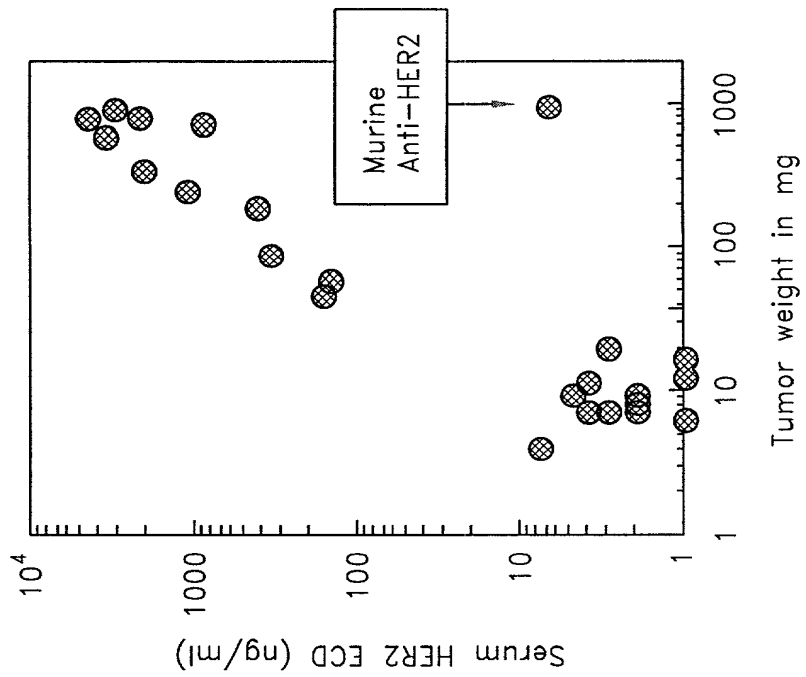


FIG. 8B



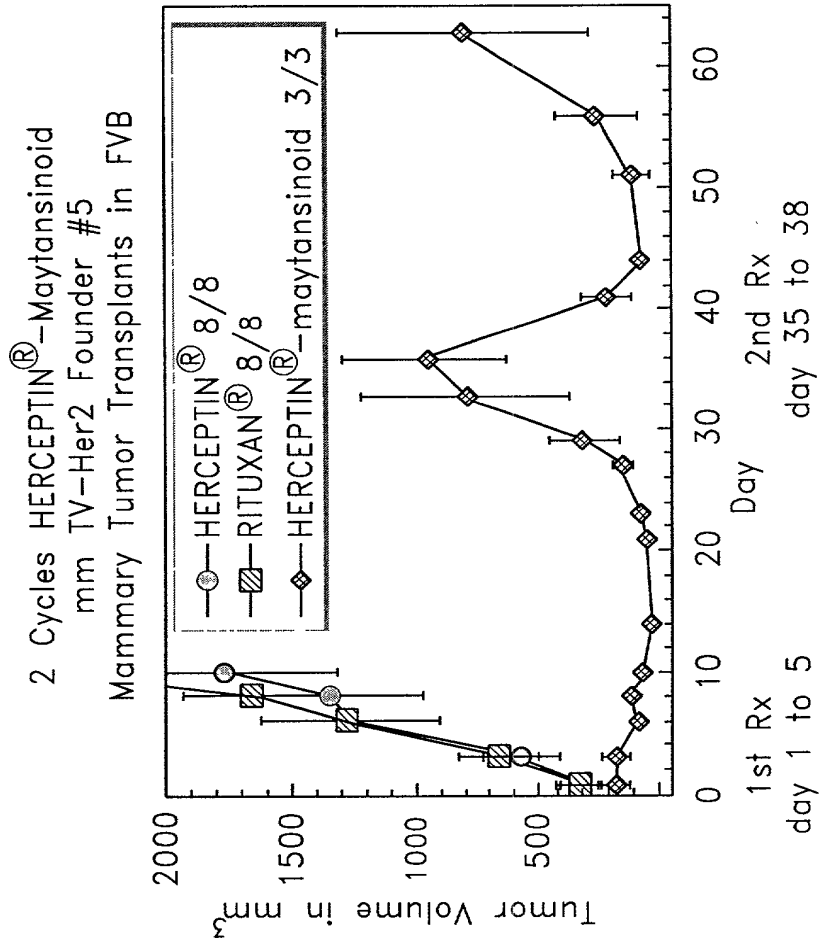


FIG. 9

HER2 Y.P. C-2 Herceptin Both

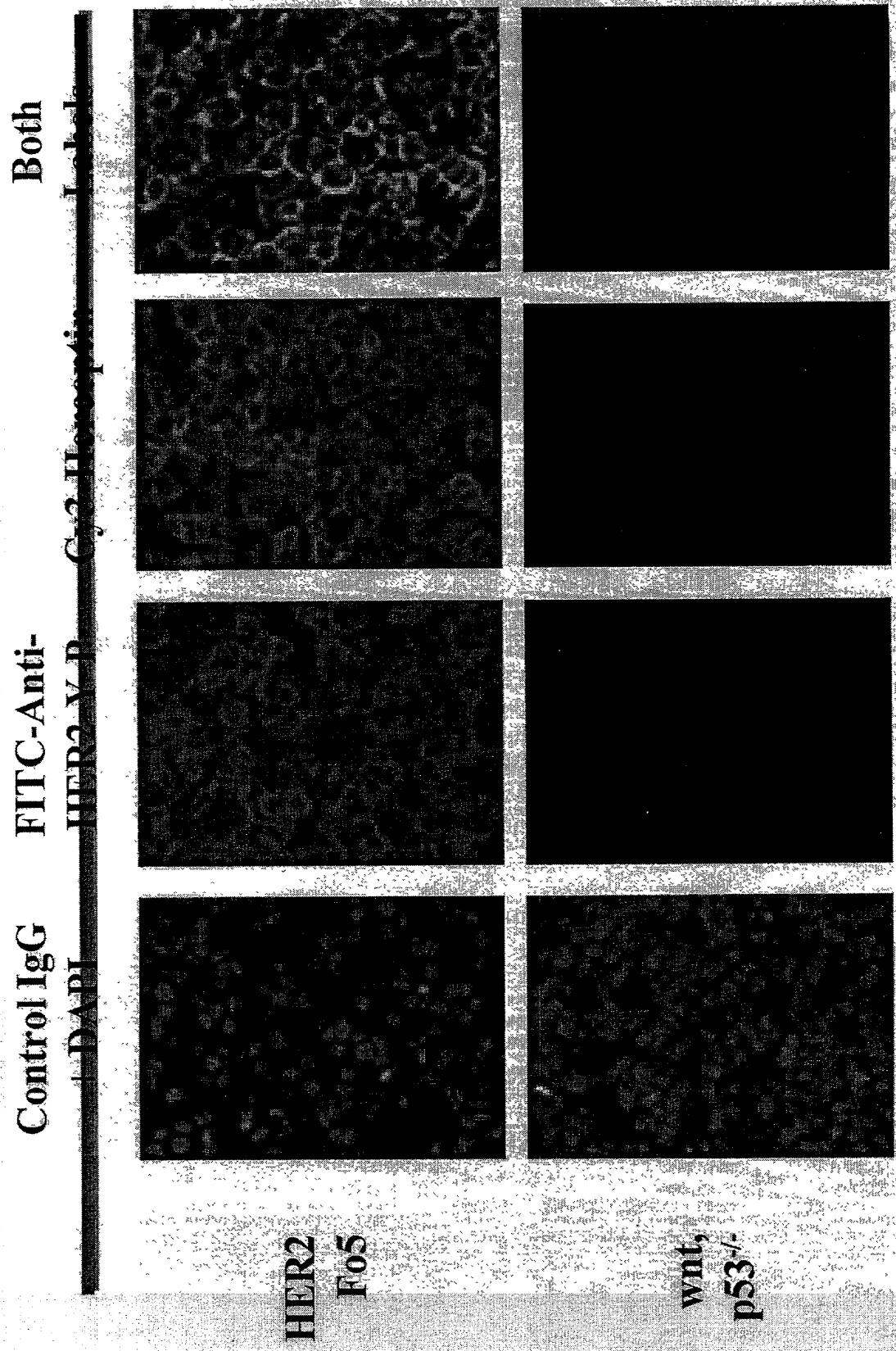


FIG. 10

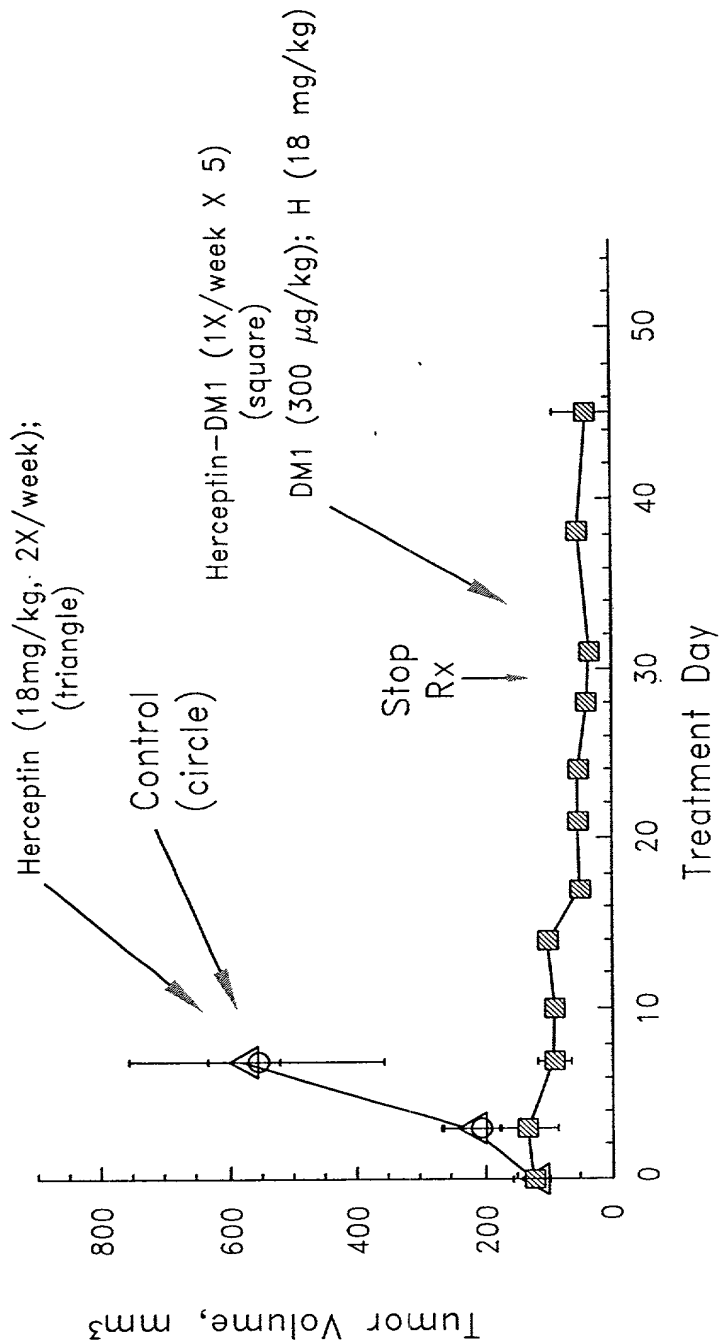


FIG. 11

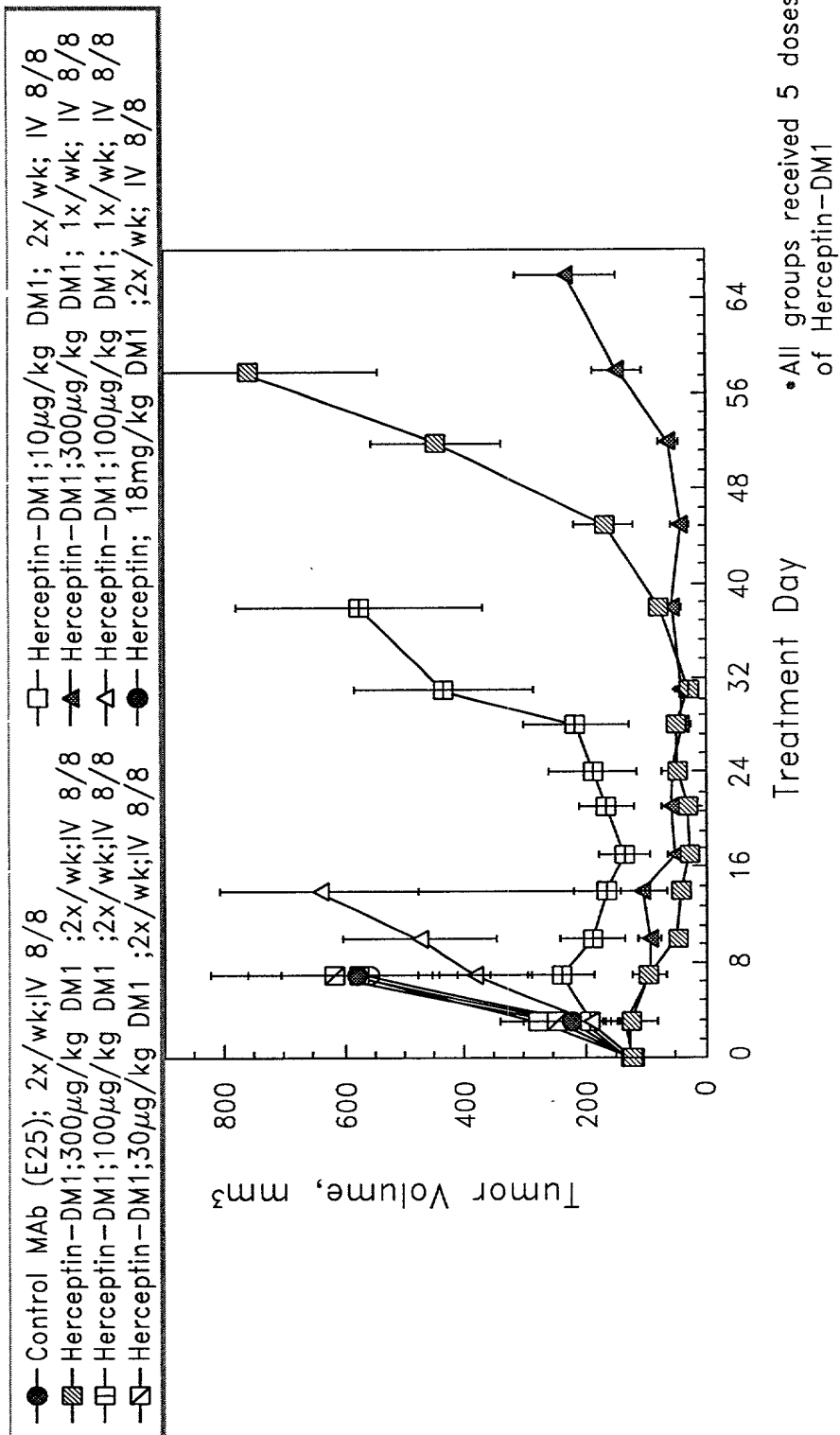


FIG. 12

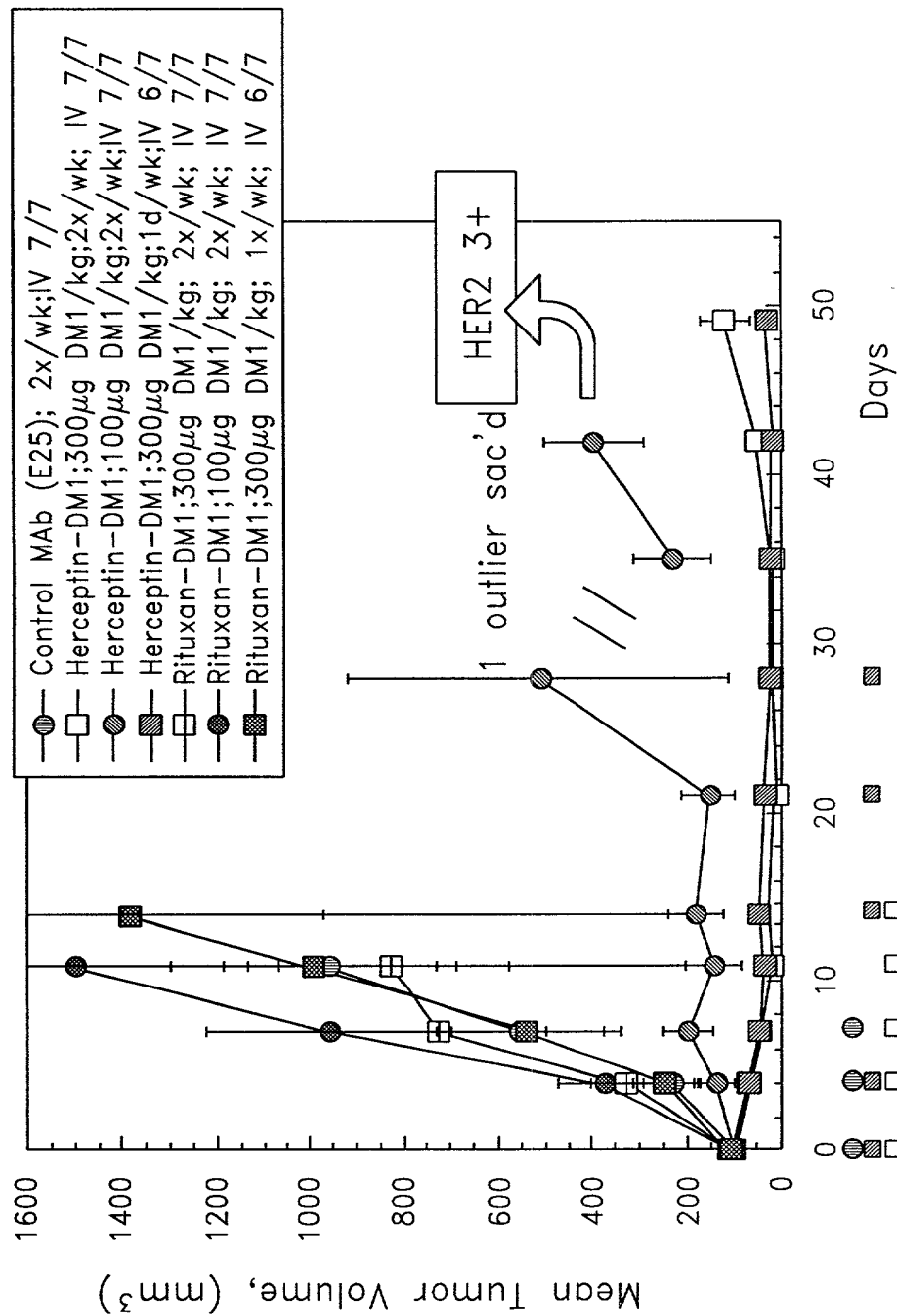


FIG. 13

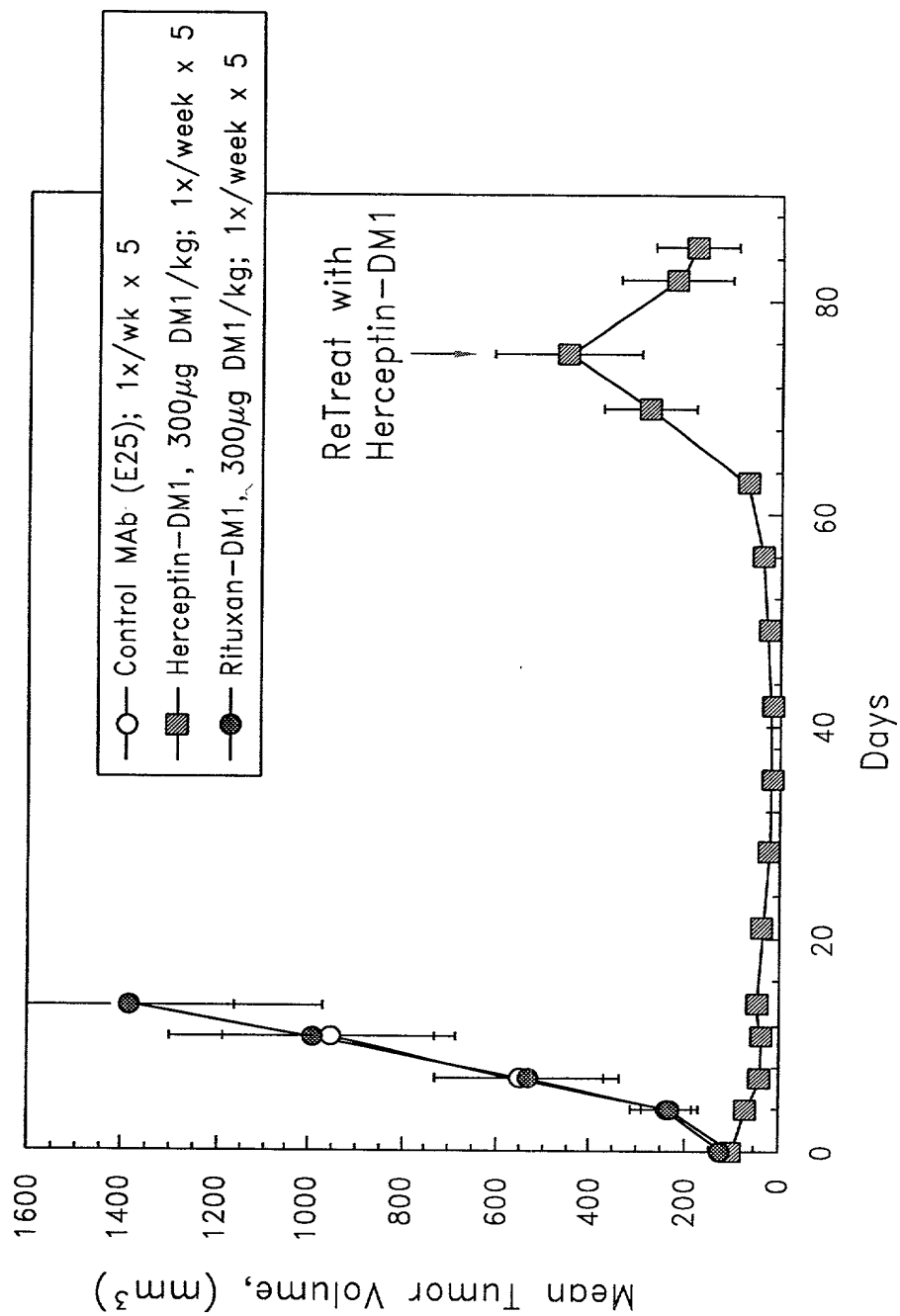


FIG. 14